REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed although claims 9-12, 14, and 15 are indicated as being only objected to for being dependent on a rejected base claim but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 1, 4, 7-12, 14, and 15 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claim 9, which is only objected to as being dependent from a rejected claim, is now rewritten in independent form including all the limitations of the base claim and any intervening claims. As claims 10-12, 14 and 15 are all dependent from claim 9, it is believed that claims 9-12, 14, and 15 are now allowable.

Claim 8 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that claim 8 depends from cancelled claim 6 and is thus vague and indefinite. Claim 8 is now amended to be dependent from claim 4, thereby obviating this rejection.

Claims 1, 4, 7, and 8 have been rejected under 35 U.S.C. §102(b) and (e) (2) as being anticipated by Tawashi, U.S. Patent 5,648,101. This rejection is respectfully traversed.

Tawashi discloses at column 4, lines 55-56 (specifically cited by the examiner) that:

> The use of the osmotic pumping technique for the delivery of a constant rate of NO is more effective and safer than the use of intravenously administered sodium nitroprusside. The development of this NO delivery technology enables administration of the exact dose, establish dose response relationship, monitor the hemodynamic activity, and adjust and control the administered dose. NO will act not only as vasodilator but increases the permeability of the blood brain barrier to allow nerve growth factors and other important neurotrophic agents to reach their target cells.

With due respect to the examiner, the examiner has combined this disclosure out of context with Tawashi's disclosure at column 3, lines 42-44, that NO is an unstable molecule having a high chemical activity and a short half life of about 30 seconds and has misinterpreted the combination as a teaching of "to transiently increase the permeability of the blood brain barrier" as recited in claim 1. It should be emphasized that Tawashi is referring to the transient nature of the NO molecule itself, not the transient increase in the permeability of the blood brain barrier. This distinction is made clear to those of skill in the art in Example A of Tawashi at columns 6-7, where Tawashi discusses the osmotic pump technology which delivers a constant rate of NO to the desired site and thus provides sustained or persistent release. At column 7, lines 7-29, Tawashi teaches that a two osmotic pump system (e.g., Alzet 2001

or 2ML4 pumps) is used to mix two components which will generate NO for pumping/administration to the desired site in the animal. If the Alzet 2001 model pumps are used, the pumping rate of NO is 1 microliter per hour and the duration of the pumping is one week (column 7, lines 19-21). For the Alzet 2ML4 model pumps, the delivery rate of NO is 2.5 microliters per hour for 4 weeks. It would undoubtedly be clear to those of skill in the art that such a delivery system would provide long term disruption of the blood brain barrier throughout the regions of the brain supplied by the vascular tree which is perfused by the pump(s) rather than the transient increase recited in the present claims. Tawashi's teaching would instead lead to gross and long term permeability changes and pathology and, consequently, cannot anticipate the presently claimed invention.

Moreover, claim 4 is now amended to recite that the transient increase in permeability of the blood brain barrier by local administration of the composition results in little or no exposure outside of the local area of administration to the nitric oxide synthase-3 regulating agent. Support for this new recitation in claim 4 is found on page 15, lines 28-29 of the specification. By contrast, the Alzet osmotic pumps taught by Tawashi for use in delivery of a constant rate of NO in place of intravenously administered sodium nitroprusside (as conventionally used for administering nitrovasodilators) provides

systemic, not targeted or local, delivery into the vasculature. Consequently, such systemic delivery by the method of Tawashi would expose not only the blood brain barrier at the local area of administration to the nitric oxide synthase-3 regulating agent, but also the entire circulatory system, including a distant site such as "the big toe". Accordingly, Tawashi simply cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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